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AN AGENT FOR CYTOPROTECTION BASED ON NUCLEIC ACIDS AND/OR DERIVATIVES THEREOF

The invention relates essentially to an agent for protecting the skin cells, in particular the Langerhans' cells, from the sun, based on nucleic acid complexes (ribonucleoprotein, ribonucleotide, ribonucleoside complexes), to a cosmetic or dermopharmaceutical composition in which it is present for use by topical administration, and to novel compounds consisting, for example, of associations with preferably biological sun protecting agents, particularly those existing in the epidermis which have a direct sun protecting action, such as keratin, urocanates and certain amino acids, or an indirect action, such as tyrosine compositions, tryptophan, stimulating the biosynthesis of melanin (which is recognized as one of the best natural sun protecting agents for combating the harmful effects of solar or UV radiation).

Numerous agents for protecting the skin from the sun are already known in the prior art. For example, patent document FR-A-2 026 267 describes the use in association of uracil, cytosine, guanine and/or 5-chlorouracil as agents for protecting the skin from the sun, sun protection control tests being given by determination of the "mean protecting factor" according to SCHULZE (Parfumerie und Kosmetik 37, 310/365 (1956)). The latter document also describes combinations of these substances, which are purine or pyrimidine bases, with customary sun protecting agents such as cinnamates, in particular ethylhexyl p-methoxycinnamate.

However, these purine or pyrimidine bases are

sparingly soluble or insoluble in water.

Also, the Applicant's prior art document EP-B-10 483 discloses agents for accelerating tanning, thereby resulting in protection of the skin from the sun, which are based on arginine tyrosinate and make provision for combinations with urocanic acid or arginine urocanates. Tanning accelerators have a sun protecting effect by stimulating the formation of melanin. Also, patent document FR-A-2 579 461 describes urocanic acid amides as sun filter

Also, patent document FR-A-2 511 243 discloses the use of highly polymerized DNA, mainly in cosmetic compositions such as creams, milks or lotions, for improving the elasticity or cell regeneration. Said document refers to the possibility of protecting the skin from the harmful rays of the sun. However, in the case of the sun milk, it is proposed to add an ultraviolet-resistant sun filter and it is indicated that this must be non-sensitizing.

None of them has been described by the author.

Furthermore, various nucleic acid derivatives have been described as such, in some cases with a therapeutic application mainly for combating the asthenia due to hepatic insufficiently (see patent documents FR-A-2 329 289; FR-A-2 181 220; US-A-3 326 892; AU-B-461 034; FR-A-1 440 795; FR-A-2 354 774; FR-A-2 113 774; BSM-A-3 932; BSM-A-5 032 and BSM-A-4811).

The purpose of all the known sun protecting agents is to protect the skin from the dangers of abusive or chronic exposure to the sun, the harmful effects of which are well known to be associated mainly with ultraviolet radiation of the UVB and UVA type. These harmful effects are known to result in acute manifestations ranging from simple sunburn to skin necrosis with different degrees of burns in between, delayed effects

resulting from prolonged and repeated exposure and culminating in premature aging of the skin, and, finally, long-term carcinogenic effects on the skin following chronic UVR exposure.

Sun protection has therefore long been seen as a necessity for guarding against the harmful effects of solar radiation.

Thus numerous cosmetic products known as sun products have been marketed which are supposed to guarantee protection from the damage caused by the sun, said products being applied topically and containing a variety of sun protecting or anti-sunburn agents, representative examples of which are given in the documents mentioned above.

For consumers, the sun protecting efficacy of these "sun" products is specified on the products by way of the S.P.F. (Sun Protecting Factor) determined by photobiologists on groups of volunteers of common phototypes, according to official methods.

These methods are based in particular on visual determination of the MED (Minimum Erythemal Dosis (sic)), corresponding to the smallest dose of UVR irradiation which is capable of producing, with the aid of a solar simulator, a visible erythema, with sharply defined edges, 24 h after irradiation.

However, histological controls have shown that, well before preliminary erythemas start to appear, cell damage already occurs at UVR doses well below the MED. The SPF value is therefore inappropriate for protection of the cells from the sun. Thus it has been possible to observe the appearance, in the epidermis, of totally characteristic "Sunburn Cells", corresponding to epidermal keratinocytes injured by UVR, at doses below the MED, i.e. without the appearance of erythemas having been observed. Thus, if cell damage in the skin can appear at

UVR doses below those which produce a visible erythema, it is manifestly in one's interest not to accept a level of sun protection which makes it possible to avoid sunburn, but additionally to ensure true protection of the living cells of the epidermis and dermis from the sun, something which sun filters formulated simply on the basis of an MED of average value are unable to do well, if at all; moreover, the MED is generally not known to the users and, furthermore, is evolutive.

The following may be mentioned as principal examples of these living cells which can suffer damage by UVR:

* In the epidermis:

- the epidermal keratinocytes, which are essential for protection of the skin, and more particularly
- the Langerhans' cells, which are a fundamental component of the skin's immune defense system; they play a fundamental part in the capture and treatment of antigens:
  - exogenous antigens: for example viruses, toxic substances or sensitizing substances, and
  - endogenous antigens: abnormal or transformed epidermal cells or even malignant epidermal cells.

According to B. GILCHREST*, if the number of Langerhans' cells and their functionality (explored by the DNCB test) decrease with age in covered zones (physiological aging), this decrease with age is even greater in exposed zones compared with covered zones (actinic aging).

This deterioration with age in the number and

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* Barbara A. GILCHREST - SKIN * AGING PROCESSES - CRC Press - 1984 - pages 73, 87, 102, 103.

function of the Langerhans' cells, which is mainly associated with repeated exposure to the sun, causes a weakening of the skin's immune defense system and favors cutaneous carcinogenesis and photocarcinogenesis in particular.

- other epidermal cells which are involved: the MERCKEL cells and the melanocytes, the number and vitality of which decrease with age; this proportionately reduces the skin's capacity to protect itself from the sun by means of melanotic pigments.

* In the dermis:

- the fibroblasts-fibrocytes, which are responsible for biosynthesis of the constituent components of the dermis.

Furthermore, the present inventors set out to check whether the conventional sun preparations and, if appropriate, sun filters, such as the cinnamates and esters of PABA, are capable of having a cytotoxic or photocytotoxic effect on the living cells of the epidermis and/or dermis which they are supposed to be protecting from the sun, and particularly on the Langerhans' cells, which constitute the essential component of the skin's immune system.

Now, the present inventors were able to discover, unexpectedly, that when brought into contact with living epidermal and dermal cells under in vivo and in vitro conditions, the filters tested were not only poorly tolerated, but also exhibited a considerable cytotoxicity, particularly when controlled in vitro. As regards the Langerhans' cells, the commonly used filters behave like haptens, i.e. they block or degrade the essential function of immunological response of the Langerhans' cells. This process is evident inter alia through blocking of the HLADR site, which plays an essential part in the

recognition and presentation of antigens.

Now, the protection of cells from the sun becomes aberrant if the sun protecting agent is itself cytotoxic or interferes with function.

The observation that known sun filters tested in contact with the above-mentioned living cells are cytotoxic suggests that the risk exists not only in cell culture, but also in vivo in the case where these filters could pass through the skin simply by topical use.

Now, recent studies carried out on various cinnamic acid esters, which are common sun protecting agents, demonstrate that when they are introduced into cosmetic excipients for sun products, these filters penetrate the skin relatively quickly, but also that they are present in the bloodstream (see the pharmacy thesis by Mr. Denis CLAUS, submitted to the University of Strasbourg FRANCE (1982), entitled "Etude de la stabilité photochimique et de la pénétration cutanée d'esters de l'acide para-méthoxycinnamique" ("Study of the photochemical stability and skin penetration of paramethoxycinnamic acid esters")).

Similarly, other publications refer to sensitizations and allergic reactions (inter alia the book by J. Foussereau entitled "Les eczémas allergiques, au chapitre: Les Anti-solaires" ("Allergic eczemas, in the chapter: Anti-sunburn products"), published by éditions MASSON in 1987, in particular pages 312-319, and the article by MAYBACH published in Contact Dermatitis 1978, pages 1665-1666, entitled "Allergic Contact Photodermatitis to PABA; the article by JEANMOUGIN published in Photo-dermatoses, page 180, relating to contact allergies and photo-allergies; the article by DAVIES published in Contact dermatitis 1982, 8, pages 190-192, entitled "Acute Photo-sentivity (sic) from sunscreen 2, EE PMC; the article by Horio published in Dermatologica

1978, 156, pages 124-128, entitled "Photo Contact Dermatitis from PABA", and the article by THOMSON and MAIBACH published in Arch. Dermatology, 1977, 113, pages 1252-1253, as well.

One object of the present invention is therefore to solve the novel technical problem consisting in providing novel specific agents for protecting the cells from the sun which can be used topically for long periods, are cytocompatible and are well tolerated in normal topical use, even for prolonged periods, as are the so-called "anti-aging" products for daily use, preferably without the incorporation of conventional sun filters.

A further object of the present invention is to solve the novel technical problem consisting in providing novel sun protecting agents having a specific sun protecting activity on the cells, especially the essential cells of the epidermis and dermis, such as the keratinocytes, the fibroblasts and most particularly the Langerhans' cells.

A further object of the present invention is to solve the novel technical problem consisting in providing novel agents for protecting the cells from the sun which do not behave or essentially do not behave as haptens, i.e. they do not block the essential function of immunological response of the Langerhans' cells.

A further object of the present invention is to solve these above-mentioned novel technical problems by providing such novel agents for protecting the skin cells from the sun which are also compatible and stable in the majority of cosmetic or dermatological preparations, while at the same time preferably being water-soluble, thus permitting better penetration into the epidermal layers; this makes it possible to differentiate between bio-agents for protecting the cells from the sun and con-

ventional sun filters.

The present invention solves these novel technical problems simultaneously, for the first time, in a way which can be used on the industrial scale.

Thus, according to a first feature, the present invention provides the use in the manufacture of a medicament for protecting skin cells, in particular the Langerhans' cells, from the sun, and preferably not containing a synthetic cytotoxic sun filter, in particular of the cinnamate or PABA type or their derivatives, of at least one compound selected from the group of nucleic acid compounds and derivatives consisting of:

A - ribonucleic acids and their salts with mineral or organic bases, and preferably complex salts with basic proteins, basic amino acids or basic peptides;

B - ribonucleotides and their salt-type derivatives with mineral or, preferably, organic bases, including complex salts with basic proteins, basic amino acids or basic peptides; and

C - ribonucleosides.

The invention also provides the use of at least one compound of the aforesaid group in a cosmetic composition for protecting the skin cells from the sun, the said composition not including a cinnamate or PABA ester sun filter.

In one particular embodiment, the ribonucleic acids are in the form of salts with mineral bases which are advantageously selected from NaOH, KOH and NH_4OH, or with organic bases, in particular ethanolamines.

In another particular embodiment, the ribonucleic acids are in the form of their salts with basic proteins such as:

- histones or microproteins with a molecular weight of between about 11,000 and 24,000, which are strongly basic on account of being rich in basic amino acids of the arginine and lysine type, constituting up to 25% of the amino residues of these molecules; preferred his-

tones are those of the H1, H2A, H3 and H4 type, which are reported for example on page 818 of the book by A. LEHNINGER; such histones are found in particular in the sperm of certain fish, the leukocytes, the thymus and, more generally, all cell nuclei; and

- globins with molecular weights of between about 15,000 and about 70,000, which are rich in constituent basic amino acids of the histidine type (5 to 9%) and lysine type.

In another particular embodiment, the ribonucleic acids are in the form of their complex salts with basic amino acids which are preferably selected from L-histidine, L-arginine, L-lysine, L-hydroxylysine and L-ornithine.

In another variant, the ribonucleic acids are in the form of their salts with basic peptides.

In addition, it should be noted that the complex salts of the above-mentioned ribonucleic acids have the advantage of being water-soluble, of having a good diffusibility in the epidermis and of being able to be used at concentrations which make it possible preferably to obtain biocompatible pH values of between 5.8 and 8, the interstitial liquid medium being at a pH of about 7.4.

In another particular embodiment of the invention, the above-mentioned ribonucleotides are selected from the group of the ~~common~~ naturally occurring monoribonucleotides, i.e. the normal constituents of the corresponding nucleic acids which have a strong UV absorption capacity at wavelengths from 250 to 280 nm.

The preferred ribonucleotides are as follows:

AMP	ADP	ATP
GMP	GDP	GTP
CMP	CDP	CTP
UMP	UDP	UTP
IMP	IDP	ITP
XMP	XDP	XTP

Preferably, the above-mentioned ribonucleotides are used in the form of their salts with bases, making it possible to obtain pH values of the order of 5.8 to 8, which are biocompatible.

In one particular embodiment, the above-mentioned ribonucleotides are in the form of their salts with mineral bases which are preferably selected from NaOH, KOH and NH_4OH, or with organic bases, in particular ethanolamines. A particularly preferred example of a salt is the sodium salt of ATP because of its specific sun protecting effect on the Langerhans' cells.

In another particular embodiment, the above-mentioned ribonucleotides are in the form of their salts with basic proteins such as:

- histones or microproteins with a molecular weight of between about 11,000 and 24,000, in particular histones of the H1, H2A, H3B, H3 and H4 type defined above; and
- globins or proteins ~~copulas of~~ formed by coupling hemoglobins and myoglobins with molecular weights of between about 15,000 and about 70,000.

In another particular embodiment of the invention, the above-mentioned ribonucleotides are in the form

of their salts with basic amino acids, in particular one or more basic amino acids selected from the group consisting of L-histidine, L-arginine, L-ornithine, L-hydroxylysine and L-lysine.

In another variant, the ribonucleotides are in the form of their salts with basic peptides.

In another particular embodiment, the above-mentioned ribonucleosides are selected from the group consisting of the ~~common~~ naturally occurring monoribonucleosides, i.e. the normal constituents of the corresponding nucleic acids which have a strong UV absorption capacity at wavelengths from 250 to 280 nm, and preferably:

RIBONUCLEOSIDES

- Adenosine
- Cytidine
- Guanosine
- Inosine
- Uridine
- Xanthosine

The advantage of the ribonucleosides is that they mostly have, as such, pH values compatible with the physiology of the skin cells, i.e. it is not necessary a priori to form salts, complexes or biochemical combinations with basic proteins, basic peptides and basic amino acids.

In certain particular embodiments, these nucleosides can be associated or combined with one or more of the above-mentioned nucleoproteins or ribonucleotides and their salts, in proportions calculated to give biocompatible pH values of between 5.8 and 8.

It is understood that, according to the invention, it is preferred to use water-soluble agents for

protecting the cells from the sun, having a good diffusibility in the epidermis, at concentrations which make it possible to obtain biocompatible pH values, i.e. pH values of between 5.8 and 8.

It should be noted that the nature of the RNA or the polyribonucleotides used to form the derivatives according to the invention is arbitrary. In fact, it is possible to use starting polyribonucleotides whose secondary or tertiary structure is preserved, but also ribonucleic acids resulting from the more or less partial denaturation of polyribonucleotides, since this more or less partial denaturation does not present problems. Thus it is possible to use acids whose primary structure can be preserved to the maximum extent, or the product of more or less controlled denaturation-degradation of these primary structures, resulting in fragments of primary structure ranging from poly- to oligo- and to mononucleotides and/or to the corresponding poly-, oligo- or mono-ribonucleosides.

This more or less partial denaturation does not present problems for the formation of the derivatives according to the invention which are used as agents for protecting the cells from the sun, since the purpose of this use is not in any way to translate the original genetic message of the RNA used to prepare the derivatives according to the invention.

It follows from the above that the purpose of the topical use of the derivatives according to the invention is to exert sun protecting effects on the cells by depositing the compounds according to the invention on or in the surface layers of the skin.

Said compounds thus act as chromophores or the most advanced passive targets, which will absorb or trap the energy of the radiation, competitively and preferentially, thereby preventing the radiation from reaching

the potential targets which must actually be protected from irradiation damage, said potential targets consisting of the active cell organelles and constituent macromolecules.

In addition, the presence of a substantial amount of the compounds according to the invention, including poly-, oligo- and mono-ribonucleotides, salts, complexes, combinations and derivatives of poly-, oligo- and mono-ribonucleosides, is perfectly tolerated by the cells because they are naturally present in a high percentage of between 5 and 15% relative to the dried weight of the living cells, and because they are normally present in the horny epidermal layers.

The compounds according to the invention are therefore biological substances which are homologous or analogous to the substances naturally present in the epidermis.

It is preferred to use derivatives of ribonucleic acid or RNA constituents, rather than DNA derivatives, because of the fact that:

- RNA's and derived constituents are naturally present in the eukaryotic cells at concentrations which are usually 2 to 8 times greater than those of DNA derivatives, and thus bear a closer resemblance to the physiological medium of the cells and tissues;
- RNA's and ribonucleic acid derivatives appear to be less sensitive to UVB irradiation;
- RNA's are more labile than DNA's to depolymerization and partial hydrolysis of their molecule to nucleotides, which favors protection of the skin cells from the sun; and
- RNA's are as essential to normal functioning of the skin cells as are DNA's and the proteins of these cells themselves.

In another particular embodiment of the inven-

tion, the agents according to the invention for protecting the skin cells from the sun also comprise derivatives of urocanic acid or urocanoproteins, because there is a synergistic effect between these derivatives and the above ribonucleoprotein, ribonucleotide and ribonucleoside compounds.

These derivatives of urocanic acid or urocanoproteins are simple or complex salts of urocanic acid or derivatives of urocanic acid with certain proteins, peptides and amino acids.

These derivatives of urocanic acid or urocanoproteins in the form of complex salts are preferably obtained by combining urocanic acid with:

a) basic proteins and advantageously histones or globins, in particular those defined above;
b) ribonucleotides such as ~~light-absorbing~~ AMP, ADP and ATP;
c) basic peptides; and
d) basic amino acids and preferably L-histidine, L-arginine, L-lysine, L-hydroxylysine and L-ornithine,

taken by themselves or in combination.

It will be understood that the purpose of these biochemical combinations is to produce biological complex salts which are soluble in water, in contrast to urocanic acid, which is sparingly or insufficiently soluble in water, and more cytocompatible than are the urocanates of Na and K.

These urocanic acid derivatives develop a very strong UVR-absorbing effect, especially in the 265 and 290 to 320 nm bands, these compounds being all the more UV-absorbing if they are associated with ribonucleotides, proteins, peptides and amino acids, which are themselves light-absorbing ~~and cover an~~ in the absorption band ranging from 265 to 320 nm.

They are of value by virtue of being soluble and

markedly substantive and of the fact that their solutions can be adjusted to physiological pH values of 6.0 to 8.0, according to the proportions of each of the constituents.

Another unexpected and particularly advantageous effect of the agents of the invention for protecting the cells from the sun is the fact that combining the urocanic acid derivatives with the agents of the invention for protecting the cells from the sun reproduces a natural process which the skin uses to defend itself against the sun. It can be observed that the proportion of urocanic acid salts and complexes increases considerably, by a factor of up to 10, in the epidermis, and particularly in the reservoir part of the horny layer, after irradiation by the sun and following thermal stimulation of the sweat glands by solar infrared radiation.

According to the invention, the preferred urocanic acid derivatives are the urocanoprotein complexes, namely the complexes of urocanic acid with histones, peptides, basic amino acids and nucleotides, which are more cytophilic than the alkali metal or alkaline earth metal salts or derivatives.

In another particular embodiment of the invention, the agents according to the invention for protecting the skin cells also comprise amino acids and peptides or proteins.

Advantageously, these amino acids and these peptides and proteins are selected from:

1) one or more of the 20 common amino acids ~~usually found~~ which occur naturally in proteins, as per the following list:

- Amino acids forming part of the complexes and combinations mentioned above: L-histidine, L-arginine, L-lysine, L-citrulline, L-ornithine and L-hydroxylysine.
- Aromatic amino acids: L-tyrosine, L-phenylalanine and L-tryptophan. These are very advantageous as they themselves have a substantial UVR-absorbing effect in

the 280 nm band.

- Dicarboxylic amino acids: L-glutamic acid and L-aspartic acid.
- Cyclic amino acids: L-proline* (L-hydroxyproline).
- Monocarboxylic amino acids: glycine, alanine, L-valine*, L-leucine* and L-isoleucine.
- "Alcohol" amino acids: L-serine* and L-threonine*.
- "Amidated" amino acids: L-glutamine* and L-asparagine.
- Sulfur-containing amino acids and sulfur-containing oligopeptides: L-cysteine*, L-methionine* and cystine*.

*Epidermal amino acids which are abundant in keratin and whose sun protecting capacity is known.

2) One or more of the peptides and proteins ~~usually found~~ which occur naturally in cells, and/or peptides resulting from the acid, basic or enzymatic hydrolysis of polypeptides and/or proteins, scleroproteins and soluble proteins.

An example is GLUTATHION, a perfectly water-soluble tripeptide which is usually present in a high concentration (5 mM) in all living tissues and which plays an important part in the intracellular transport of amino acids and in biological oxidation-reduction reactions.

Hormone peptides are excluded from the present invention. The following, on the other hand, are advantageously complementary:

- Scleroproteins and their partial hydrolyzates.
  Examples:
  - silk fibroin concentrations from 1 to 10%
  - collagen concentrations from 1 to 10%
  - elastin concentrations from 1 to 10%
  - hydrophilic keratins
- Soluble proteins and their partial hydrolyzates.
  Examples (in concentrations of 0.10 to 10%):
  - histones

- globins (hemoglobins and myoglobins)
- plasma proteins (for example serum albumin and serum globulins)
- partially hydrolyzed plasma proteins (enzymatic hydrolysis), or partially hydrolyzed proteins from blood plasma rich in proteins (about 8%), which can be used as a synergistic biological sun protecting solvent and biological transport vehicle by virtue of the osmotic pressure which it develops, said plasma being particularly active at its original pH of 7.4 in dissolving and diffusing the above-mentioned ribonucleic acid derivatives.

The value of these peptides and proteins is that they themselves have a light-absorbing capacity in the ultraviolet spectrum:

- in the 250 to 300 nm zone (absorption resulting mainly from the presence of the 3 aromatic amino acids; tyrosine, tryptophan and phenylalanine);
- in the 210 to 250 nm zone (absorption due especially to the amino acids cysteine, methionine and histidine); and
- in the zone below 210 nm (absorption due to the peptide linkages),

and that they can be used synergistically with all the above-mentioned nucleoproteins and all the above-mentioned urocanoproteins, boosting their capacity to protect the cells from the sun.

The present invention also provides cosmetic or pharmaceutical compositions for topical application, active

in protecting the skin cells from the sun, especially in protecting the cells from the sun and combating premature aging of the skin, and in particular in protecting the Langerhans' cells, said compositions comprising a compound selected from the group consisting of:

A - simple or complex salts of the ribonucleic acids with organic bases selected from basic proteins and basic peptides, and

B - simple or complex salts of the ribonucleotides with organic bases selected from basic proteins and basic peptides, in a cosmetic or pharmaceutical excipient, vehicle or carrier for topical application.

In these cosmetic or dermopharmaceutical compositions according to the invention, the total concentration of sun protecting agents according to the invention is usually similar to the concentrations of sun protecting agents known in the prior art and used for protecting the skin from the sun. This concentration of active principle(s) according to the invention will advantageously be between 0.01% and 10% by weight, preferably 0.1 to 3%, relative to the total weight of the cosmetic or dermopharmaceutical composition.

It will be possible to use any type of excipient normally found in such cosmetic or dermopharmaceutical compositions for use by topical administration.

According to a third feature, the present invention further relates to novel compounds which are compounds

selected from the group consisting of simple or complex salts of the ribonucleotides with organic bases selected from the basic proteins such as histone and globin and basic peptides.

In a variant, the ribonucleotides are selected from:

AMP	ADP	ATP
GMP	GDP	GTP
CMP	CDP	CTP
UMP	UDP	UTP
IMP	IDP	ITP
XMP	XDP	XTP

The salts of ribonucleotides with organic bases, including the complex salts with basic proteins, and basic peptides as defined above, are prepared according to a conventional acid-base reaction.

The cosmetic and/or dermopharmaceutical compositions of the invention may be prepared by a process which comprises incorporating at least one agent for protecting the skin cells from the sun, as defined above, into a cosmetologically and/or pharmaceutically compatible excipient, vehicle or carrier.

Further objects, characteristics and advantages of the invention will be made clear by the following explanatory description referring to a number of Examples

of the invention, which are given simply by way of illustration and cannot in any way limit the scope of the invention. In the present description and especially in the Examples, all the percentages are given by weight, unless indicated otherwise.

EXAMPLE 1

Preparation of a ribonucleate of a mineral base

A potassium ribonucleate, for example, is prepared in the following manner:

5.7 ml of 0.5 N KOH are used to dissolve 1 g of RNA which has first been dispersed in 2 g of distilled water.

This gives a solution of pH 6.85.

The ribonucleic acid is added over a few minutes, with vigorous stirring.

The potassium ribonucleate prepared in this way is separated off in the following manner:

To obtain the potassium ribonucleate in the form of a white pale yellow powder, it suffices to lyophilize this solution rapidly. The following physicochemical characteristics are obtained:

- ultraviolet spectrum (distilled water) = maximum 260 nm
- pH (aqueous solution) prepared as above = 6.85.

The sodium or ammonium ribonucleates are prepared in the same manner from the corresponding mineral bases, namely NaOH and NH_4OH.

EXAMPLE 2

Proteide ribonucleate

Histone ribonucleate is prepared by using, for example, commercially available RNA (CODEX grade).

An aqueous solution of histone (type IV, very rich in arginine) is prepared.

The RNA is added to this aqueous solution in small amounts, with stirring, and stirring is then continued until dissolution is complete and a pH of 6.8 is obtained.

The histone ribonucleate obtained is separated off as follows: by lyophilization or by precipitation with 96° ethanol. Centrifugation - washing with anhydrous ethanol - vacuum drying. Wavelength of ultraviolet spectrum: 258 - 262 nm.

EXAMPLE 3

Ribonucleate of a basic amino acid

The ribonucleates of arginine, histidine and lysine are prepared.

3 - A - Arginine ribonucleate

- In an Erlenmeyer flask, 0.665 g of L-arginine is dissolved in 100 ml of distilled water, with stirring.
- 1.335 g of CODEX RNA are added gradually, in small portions, at laboratory temperature, with stirring.
- Stirring is continued until dissolution is complete (about 1 h).
- The liquid obtained is filtered and dehydrated, for example by lyophilization: a white powder is obtained (yield: about 95%).

· Ultraviolet spectrum (distilled water): maximum 258 nm

· pH (distilled water) : 6.3.

3 - B - Histidine ribonucleate

- In an Erlenmeyer flask, 0.947 g of L-histidine is dissolved in 100 ml of distilled water, with stirring.
- 1.053 g of CODEX RNA are added gradually, in small portions, at laboratory temperature, with stirring.
- Stirring is continued until dissolution is complete (about 12 h).
- The liquid obtained is filtered and dehydrated, for example by lyophilization: a white powder is obtained (yield: about 95%).

· Ultraviolet spectrum (distilled water): maximum 258 nm

· pH (distilled water) : 6.4.

3 - C - Lysine ribonucleate

- In an Erlenmeyer flask, 0.619 g of L-lysine is dissolved in 100 ml of distilled water, with stirring.
- 1.481 g of CODEX RNA are added gradually, in small portions, at laboratory temperature, with stirring.
- Stirring is continued until dissolution is complete (about 1 h).
- The liquid obtained is filtered and dehydrated, for example by lyophilization: a white powder is obtained (yield: about 95%).

· Ultraviolet spectrum (distilled water): maximum 258 nm

· pH (distilled water) : 6.2.

EXAMPLE 4

Ribonucleotidate of a mineral base

Following the general procedure described in Example 1, the following ribonucleotidates of a mineral base are prepared:

4 - A · Sodium cytidine monophosphate
4 - B · Sodium uridine monophosphate
4 - C · Sodium inosine monophosphate
4 - D · Sodium adenosine diphosphate
4 - E · Sodium adenosine triphosphate
4 - F · Sodium guanosine monophosphate
4 - G · Sodium adenosine monophosphate

EXAMPLE 5

Protein ribonucleotidate

The following protein ribonucleotidates are prepared by the procedure given below:

- Histone cytidine monophosphate.

The preparation is carried out as follows: As cytidine monophosphate and histone are very soluble in water, it suffices to prepare 1% solutions of both and mix them until a pH of between 6 and 7 is obtained, and then to lyophilize the resulting preparation.

Mean UV absorption = 270 nm.

EXAMPLE 6

Peptide ribonucleotidate

The following peptide ribonucleotidates are prepared:

- Protamine cytidine monophosphate by the same process as in Example 5.

EXAMPLE 7

Amino acid ribonucleotidate

The following ribonucleotidates of basic amino acids are prepared:

7 - A - Arginine cytidine monophosphate

- In an Erlenmeyer flask, 0.857 g of L-arginine is dissolved in 100 ml of distilled water, with stirring.
- 1.143 g of cytidine monophosphate are added gradually,

in small fractions, at laboratory temperature, with stirring.

- Stirring is continued until dissolution is complete.
- The solution obtained is filtered and dehydrated, for example by lyophilization.
- A beige powder is obtained (yield: about 95%).
  - Ultraviolet spectrum (distilled water): maximum 272 nm
  - pH (distilled water) : 6.2.

7 - B - Histidine cytidine monophosphate

- In an Erlenmeyer flask, 1.07 g of L-histidine are dissolved in 100 ml of distilled water, with stirring.
- 0.93 g of cytidine monophosphate is added gradually, in small portions, at laboratory temperature, with stirring.
- Stirring is continued until dissolution is complete.
- The solution obtained is filtered and dehydrated, for example by lyophilization.
- A beige powder is obtained (yield: about 95%).
  - Ultraviolet spectrum (distilled water): maximum 272 nm
  - pH (distilled water) : 6.2.

7 - C - Arginine adenosine triphosphate

- In an Erlenmeyer flask, 0.966 g of L-arginine is dissolved in 100 ml of distilled water, with stirring.
- 2.034 g of sodium adenosine triphosphate are added gradually, in small fractions, at laboratory temperature, with stirring.
- Stirring is continued until dissolution is complete.
- The solution obtained is filtered and dehydrated, for example by lyophilization.
- A beige powder is obtained (yield: about 95%).
  - Ultraviolet spectrum (distilled water): maximum 260 nm
  - pH (distilled water) : 6.7.

7 - D - Histidine adenosine triphosphate

- In an Erlenmeyer flask, 1 g of L-histidine is dissolved in 100 ml of distilled water, with stirring.
- 1 g of sodium adenosine triphosphate is added gradually, in small portions, at laboratory temperature, with stirring.
- Stirring is continued until dissolution is complete (about 1 h).
- The solution obtained is filtered and dehydrated, for example by lyophilization.
- A beige powder is obtained (yield: about 95%).
  - Ultraviolet spectrum (distilled water): maximum 259 nm
  - pH (distilled water) : 6.6.

EXAMPLE 8

Ribonucleosides

The following ribonucleosides are commercially available:

8 - A · Adenosine
8 - B · Cytidine
8 - C · Inosine
8 - D · Uridine
8 - E · Uridine/cytidine (50/50)

EXAMPLE 9

Protein urocanate

Histone urocanate is prepared by following a similar procedure to that used for the preparation of protamine urocanate described in Example 10, except that the operating temperature is <50°C.

EXAMPLE 10

Peptide urocanate

Protamine urocanate is prepared in the following

manner:

- In an Erlenmeyer flask, 1.40 g of protamine are dissolved in 100 ml of distilled water, with stirring.
- 1.40 g of urocanic acid are added gradually.
- Stirring is continued at 70°C until dissolution is complete.
- The solution obtained is filtered and dehydrated, for example by lyophilization.
- A beige powder is obtained (yield: about 90%).
  - Ultraviolet spectrum (distilled water): maximum 269 nm.

EXAMPLE 11

Urocanate of a basic amino acid

The urocanates of arginine and histidine are prepared in the following manner:

- Arginine urocanate
- 720 g of methanol and 135 g of distilled water are introduced into a reactor equipped with a reflux device and 69 g of urocanic acid and 87 g of arginine are added, with stirring.
- The reaction mixture is heated slowly and heating is continued up to the reflux temperature; stirring is maintained until precipitation is complete.
- The mixture is cooled and then centrifuged and the product is dried (yield: about 90%).
  - Ultraviolet spectrum (distilled water): maximum 267 nm
  - pH (distilled water) : 7.4.
- Histidine urocanate described in the prior art
- 720 g of methanol and 135 g of distilled water are introduced into a reactor equipped with a reflux device and 69 g of urocanic acid and 78.57 g of histidine are added, with stirring.
- The reaction mixture is heated slowly and heating is

continued up to the reflux temperature; stirring is maintained until precipitation is complete.

- The mixture is cooled and then centrifuged and the product is dried (yield: about 90%).

· Ultraviolet spectrum (distilled water): from 260 to 268 nm.

There follows a series of Examples of compositions in the form of a soluble amorphous powder with which aqueous solutions can be prepared in distilled water at various concentrations, said solutions having biocompatible pH values of between 6 and 7.5, for example.

EXAMPLE 12 (Composition Example)

Histidine ribonucleate	31.65
Histidine hydrochloride	18.33
Partial hydrolyzate of lyophilized collagen	50.02
Ultraviolet spectrum (distilled water)	from 260 to 268 nm, depending on the nature of the collagen
pH	6.0 - 6.8

EXAMPLE 13

Composition	amorphous powder form
Histidine ribonucleate	31.65
Cytidine uridine	16.65
Histidine hydrochloride	18.33
Hydrolyzate of dehydrated collagen	33.37

EXAMPLE 14

Composition	amorphous powder form
Histidine ribonucleate	47.83
Sodium ribonucleate	8.15

Arginine urocanate	16.66
Uridine/cytidine	1.32
Hydrolyzate of dehydrated collagen	26.04

EXAMPLE 15

Composition	amorphous powder form
Arginine ribonucleate	26.00
Histidine urocanate	15.63
Arginine hydrochloride	1.03
Histidine hydrochloride	24.67
Hydrolyzate of dehydrated collagen	17.02
Uridine/cytidine	16.65

EXAMPLE 16

Composition	amorphous powder form
Histidine ribonucleate	31.65
Histidine	18.33
Arginine urocanate	16.65
Uridine/cytidine	16.65
Hydrolyzate of dehydrated collagen	16.72

EXAMPLE 17

Composition	amorphous powder form
Histidine ribonucleate	31.65
Histidine	18.33
Arginine urocanate	16.65
Hydrolyzate of lyophilized collagen	33.37

EXAMPLE 18

Composition	amorphous powder form
Arginine ribonucleate	37.50
Arginine urocanate	33.67
Histidine urocanate	20.00
Glutathion	1.25
L-tyrosine	3.00

L-phenylalanine	0.50
L-tryptophan	0.75
L-histidine CLH	1.33

pH in distilled water = 6.5 - 7

EXAMPLE 19

Composition	amorphous powder form
Arginine ribonucleate	37.50
Arginine urocanate	35.67
Histidine urocanate	20.00
Glutathion	1.25
L-tyrosine/L-phenylalanine/ L-tryptophan	4.25
Histidine hydrochloride	1.33

EXAMPLE 20

Composition	amorphous powder form
Adenosine	0.04
Guanosine	0.04
Inosine	0.04
Cytidine	0.04
Uridine	0.04
Glucose	9.40
Arginine urocanate	15.00
Hydrolyzate of lyophilized blood plasma	75.04

EXAMPLE 21

Sodium ribonucleate	20.00
Arginine CMP	1.70
Histidine GMP	1.70
UMP, sodium salt	1.00
Glucose	2.50
Keratin hydrolyzate	73.10

The basic compositions constitute compositions of

agents of the invention for protecting the cells from the sun and can be incorporated as active principles, at doses of between 0.01% and 5%, exceptionally of +10% and preferably of 0.10 - 3%, into dermatological, cosmetological and dermopharmaceutical preparations to form cosmetic or dermopharmaceutical compositions according to the invention.

This incorporation is extremely straightforward and usually involves dissolution in the aqueous phase of these preparations at temperatures of between 20°C and 70°C.

It is possible to use any type of excipient normally used in such cosmetic or dermopharmaceutical compositions containing water. Said compositions can be aqueous lotions, aqueous gels, emulsions, ointments, creams or salves or presented in the form of ordinary capsules or gelatin capsules.

Moreover, these active principles can be incorporated into liposomes, micelles and other forms of microencapsulation in order to accelerate or delay their penetration.

An Example of the preparation of a cosmetic and/or dermopharmaceutical composition containing one of the above-mentioned compositions forming the subject of the invention is given below.

The other compositions can obviously be used in the same way.

For example, the composition according to Example 13 is incorporated at a dose of 1% into the following emulsion:

Propylene glycol stearate SE	1.00
Paraffin oil	7.70
Stearin	1.50
Stearyl alcohol	0.40
Glycerol	4.00

Carbomer 934	0.10
Triethanolamine	0.80
Preservative	qs
Distilled water	qs 100.00

EXPERIMENTAL RESULTS

To illustrate and demonstrate the advantages of the biological agents according to the invention for protecting the cells from the sun, they were subjected to experimental studies by comparison with the conventional sun protecting agents with the aim of evaluating:

- on the one hand their intrinsic cytotoxicity, and
- on the other hand their capacity to protect the cells from the sun when in contact with the cells.

Thus the results obtained for some of the compounds mentioned in the Examples on the previous pages are collated in the following three Tables.

It should be noted that, as regards the capacity of these compounds to protect the skin from the sun, relating to the methods of SCHULTZE or variants based on the MED, i.e. the irradiation dose at which a limited erythema appears, the strengths of anti-sunburn protection which could be obtained would correspond to low to medium factors.

By contrast, as regards assessment of the protection of the cells from the sun by contact in vitro, the agents for protecting the cells from the sun which form the subject of the present claims are devoid of cytotoxicity at the useful concentrations and afford true protection of the cells from the sun, and essentially UV-B, at levels of irradiation which can normally be tolerated by every user, in terms of their MED.

It should also be noted that a comparative test performed with a sodium salt of deoxyribonucleic acid does not afford significant protection of the cells from the sun. It is therefore surprising and not at all obvious to those skilled in the art that the organic derivatives of ribonucleic acid according to the invention do have a sun protecting effect on the cells.

- It is further known that UV-B rays cause morphological and functional degradation of the Langerhans' cells, and it is known that the common sun filters of the cinnamate and PABA type do not prevent this degradation.
- Likewise, it is known that UV-B rays cause a drop in the ATP-ase activity of the Langerhans' cells and that this degradation cannot be prevented by the above-mentioned sun filters.
- These same filters are inactive in ensuring protection of the Langerhans' cells against degradation and negation of the response to the DNFB immunological test by UV-B rays.

PROTOCOL type I

LD$_{50}$ on MRC5 fibroblasts in vitro

- The MRC5 fibroblasts are inoculated on to EMEM complemented with fetal calf serum (5%).

- After 24 h, the medium is replaced with a saline solution (PBS) of the test product (in the case of the filters EHPMC and EHPAB, a stock solution is prepared).

- By introducing increasing dilutions of the test substance (from 0.01% to 0.03%), a sufficient number of dishes are prepared for carrying out a series of ex-

ploratory tests.

- All the dishes are then incubated at 37°C for 2 h.
- The saline solution is then replaced with the usual growth medium (EMEM + 5% of FCS).
- After 72 h, the cell cultures are stained.
- The number of living cells is evaluated by measuring the intensity of staining in each dish with an electronic image analyzer.
- The LD_{50} corresponds to the dose of test product which is just sufficient to inhibit the cell growth rate by 50% relative to the control.

PROTOCOL type II

Toxicity on MRC5 fibroblasts

- The MRC5 cells are inoculated on to conventional culture medium.
- After 24 h, they are brought into contact with the test product, which has first been dissolved in PBS.
- The solution is then replaced with the growth medium consisting of EMEM + 5% of FCS.
- After 3 days, the growth rate is evaluated:
  - by measuring the staining with an electronic image analyzer

  or
  - by measuring the level of intracellular ATP.

PROTOCOL type III

LD50 on epidermal keratinocytes in vitro

- The isolated epidermal keratinocytes are cultivated on dishes (1st explantation culture) in DMEM containing 10% of FCS.

- After 24 h, the above culture medium is replaced with a saline solution enriched in amino acids (= DMEM) of the test product.

- A sufficient number of dishes are prepared for producing a series of increasing dilutions of the test substance.

- All the dishes are incubated at 37°C for 3 days.

- The intracellular adenosine triphosphate* is then extracted and determined in each dish by a bioluminescence technique.

- The toxicity of each substance studied is estimated as a percentage relative to the control medium (DMEM).

- The lethal dose (LD_{50}) is determined graphically as the minimum dose of product which reduces the level of ATP by 50% relative to the control.

LD_{50} CYTOTOXICITY STUDY

REFERENCE	Ex. n°	MRC5 fibroblasts in culture (in vitro)		Epidermal keratinocytes in culture (in vitro)	
		LD_{50} in g%	Protocol type	LD_{50} in g%	Protocol type
2-Ethylhexyl 4-methoxycinnamate (EHPMC)		0.015	I	0.038	III
2-Ethylhexyl 4-dimethylaminobenzoate (EHPAB)		< 0.01	I	0.014	III
Potassium ribonucleate	1	> 1	II	> 2	III
Arginine ribonucleate	3 A	> 2	II	> 2	III
Histidine ribonucleate	3 B	> 2	II	> 2	III
ATP, Na	4 E	> 0.5	II	0.2	III
Histidine cytidine monophosphate	7 B	1	II	0.76	III
Inosine	8 C	> 2	II	> 2	III
Composition, Ex. 13	13	> 3	II	> 2	III
Composition, Ex. 18	18	1.2	II	1.25	III

CYTOTOXICITY STUDY on LANGERHANS' CELLS (L.C.)

REFERENCE	Ex. n°	Concentration %	Cytotoxicity as percentage of L.C. destroyed	Protocol type
2-Ethylhexyl 4-methoxycinnamate (EHPMC)		0.03	79 - 80%	V
2-Ethylhexyl 4-dimethylaminobenzoate (EHPAB)		0.01	35%	V
Potassium ribonucleate	1	1	17%	V
Arginine ribonucleate	3 A	1	32%	V
Histidine ribonucleate	3 B	5	7%	V
ATP, Na	4 E	0.2	10%	V
Histidine cytidine monophosphate	7 B	0.5	34%	V
Inosine	8 C	1	33%	V
Composition, Ex. 13	13	3	32%	V
Composition, Ex. 18	18	0.5	6%	V

- The cytotoxicity on L.C. is evaluated as the percentage of the number of cells negated in the presence of the test substance, relative to the initial number of L.C. HLADR +.

- This test is performed on a suspension of L.C. originating from an epidermal biopsy treated immediately, allowing for the difficulties in cultivating the L.C.

CALCULATION of the CYTOTOXICITY (see Protocol V)

$$\frac{\text{N-batch 1 - N-batch 3}}{\text{N-batch 1}} \times 100$$

PROTOCOL IV

Evaluation of the capacity of substances to protect the cells from the sun, in contact with MRC5 fibroblasts

- The purpose of this study is to evaluate the capacities of various substances to protect the cells from the sun, on the growth of MRC5 fibroblasts, in culture in vitro, when they are irradiated by a UVB source.
- The cells are inoculated at a low rate.
- After 24 h, the MRC5 cells are covered with a solution of the test substance in PBS and then irradiated with a defined dose (in mJ/cm^2) of UVB.
- The saline solution is then replaced with the growth medium consisting of EMEM + 5% of FCS.
- After 72 h, the cell cultures are stained and the growth rate is evaluated by electronic image analysis.

PROTOCOL type V

Study of the capacity of substances to protect the cells from the sun, in contact with Langerhans' cells

Microscopic counting of the Langerhans' HLA-DR+ cells

- A suspension of epidermal cells is prepared from a skin biopsy.
- This cell suspension is divided into 2:

1/ one part serves as the control, only PBS buffer

being added:
a) 1st batch not irradiated
b) 2nd batch irradiated by UVB (x mJ/cm^2)

2/ the other part receives a solution of the test substance in PBS buffer:
a) 3rd batch not irradiated
b) 4th batch irradiated by UVB (x mJ/cm^2)

- The 4 above-mentioned batches of epidermal cells containing the Langerhans' cells are then labeled by immunocytochemistry (labeling of the specific HLA-DR antigen sites of the Langerhans' cells).

- For each of the 4 batches, the HLA-DR cells are then counted microscopically.

- Results:

- 1st batch (control): This corresponds to the initial number of intact L.C.-HLA-DR+ per unit volume.

- 2nd batch: Irradiation at a given dose of UVB causes a reduction in the initial number of L.C.-HLA-DR+ per unit volume. The number of L.C.-HLADR+ remaining = N-batch 2.

- 3rd batch: The substance supposedly having a sun protecting effect on the L.C. may exhibit a specific cytotoxicity at a given concentration. The value used is that of the number of L.C.-HLADR+ remaining per unit volume, in contact with the substance at the concentration studied. The corresponding number of L.C.-HLADR+ =

N-batch 3.

- 4th batch: This makes it possible to determine the number of L.C.-HLADR+ in contact with the test substance at a concentration identical to the 3rd batch and after UVB irradiation at the same dose as the 2nd batch. The number of L.C.-HLADR+ remaining per unit volume = N-batch 4.

STUDY of the SUN PROTECTION IN CONTACT WITH THE CELLS

REFERENCE	Ex. n°	Langerhans' cells in suspension HLA-DR + SITES (in vitro)			MRC 5 fibroblasts in culture (in vitro)		
		Concentration	Capacity for protecting the cells from the sun *	Protocol type	Concentration	Capacity for protecting the cells from the sun *	Protocol type
2-Ethylhexyl 4-methoxycinnamate (EHPMC)		0.03%	0	V	0.03%	1.8% NS	IV
2-Ethylhexyl 4-dimethylamino-benzoate (EHPAB)		0.01% 0.03%	+ 8% 0	V	0.02%	0	IV
Potassium ribo-nucleate	1	1%	+ 100%	V	1%	100%	IV
Arginine ribo-nucleate	3 A	1%	+ 65%	V	0.3%	58%	IV
Histidine ribo-nucleate	3 B	5%	+ 100%	V	0.5%	96%	IV
ATP, Na	4 E	0.2% 1%	+ 47% + 100%	V V	0.50%	46%	IV
Histidine cytidine monophosphate	7 B	0.5%	+ 24%	V	0.12%	77%	IV
Inosine	8 C	1%	+ 100%	V	1%	74%	IV
Composition, Ex. 13	13	3%	+ 53%	V	2.70%	99%	IV
Composition, Ex. 18	18	0.5%	+ 81%	V	0.50%	100%	IV

*: Maximum capacity for protecting the cells from the sun = 100%
NS: not significant

CLAIMS

1. The use in the manufacture of a medicament for protecting skin cells, in particular the Langerhans' cells, from the sun, of at least one compound selected from the group of nucleic acid compounds and derivatives consisting of:

A - ribonucleic acids and their salts with mineral or organic bases;

B - ribonucleotides and their salt-type derivatives with mineral or organic bases; and

C - ribonucleosides.

2. The use of at least one compound selected from the group of nucleic acid compounds and derivatives consisting of:

A - ribonucleic acids and their salts with mineral or organic bases;

B - ribonucleotides and their salt-type derivatives with mineral or organic bases; and

C - ribonucleosides

in a cosmetic composition for protecting the skin cells from the sun, **the said composition not including a cinnamate or PABA ester sun filter.**

3. The use according to claim 1 wherein said medicament composition does not contain a synthetic cytotoxic sun filter of the cinnamate or PABA type or their derivatives.

4. The use according to claim 1, 2 or 3 of at

least one compound selected from: complex salts of ribonucleic acids with basic proteins, basic amino acids or basic peptides and complex salts of ribonucleotides with basic proteins, basic amino acids or basic peptides.

5. The use according to claim 1, 2 or 3 wherein the ribonucleic acids are in the form of salts with mineral bases or with organic bases.

6. The use according to claim 5 wherein the ribonucleic acids are in the form of salts with NaOH, KOH, NH_4OH or an ethanolamine.

7. The use according to claim 1, 2 or 3, wherein the ribonucleic acids are in the form of their salts or complexes with

- histones or microproteins with a molecular weight of between about 11,000 and 24,000; or
- globins with molecular weights of between about 15,000 and about 70,000.

8. The use according to claim 1, 2 or 3, wherein the ribonucleic acids are in the form of their complex salts with L-histidine, L-arginine, L-lysine, L-ornithine or L-hydroxylysine.

9. The use according to any one of claims 1 to 8 wherein the ribonucleotides are selected from the group of the naturally occurring monoribonucleotides.

10. The use according to any one of claims 1 to 8, wherein the ribonucleotides are selected from:

RIBONUCLEOTIDES

AMP	ADP	ATP
GMP	GDP	GTP
CMP	CDP	CTP
UMP	UDP	UTP
IMP	IDP	ITP
XMP	XDP	XTP

11. The use according to claim 9 or claim 10, wherein the ribonucleotides are in the form of their salts with bases, and the composition has a biocompatible pH value of the order of 5.8 to 8.

12. The use according to claim 11, wherein the ribonucleotides are in the form of their salts with NaOH, KOH and NH_4OH, or with an ethanolamine.

13. The use according to claim 11, wherein the ribonucleotides are in the form of their salts with:
- histones or microproteins with a molecular weight of between about 11,000 and 24,000; or
- globins or proteins formed by coupling hemoglobins and myoglobins with molecular weights of between about 15,000 and about 70,000.

14. The use according to claim 11, wherein the

ribonucleotides are in the form of their salts with L-histidine, L-arginine, L-lysine, L-ornithine and L-hydroxylysine.

15. The use according to claim 11, wherein the ribonucleotides are in the form of their salts with basic peptides.

16. The use according to any one of claims 1 to 15, wherein the ribonucleosides are selected from the group consisting of the naturally occurring monoribonucleosides.

17. The use according to any one of claims 1 to 15, wherein the ribonucleosides are selected from:

RIBONUCLEOSIDES
. Adenosine
. Cytidine
. Gyanosine
. Inosine
. Uridine
. Xanthosine

18. The use according to any one of claims 1 to 15, wherein the ribonucleosides are associated or combined with one or more nucleoproteins or ribonucleotides and their salts, in proportions to give a biocompatible pH value of between 5.8 and 8.

19. The use according to any one of claims 1 to 18,

of also derivatives of urocanic acid or urocanoproteins in the form of simple or complex salts of urocanic acid or derivatives of urocanic acid with proteins, peptides and amino acids.

20. The use according to claim 19, wherein the derivatives of urocanic acid or urocanoproteins in the form of complex salts are obtained by combining urocanic acid with:

a) basic proteins;

b) ribonucleotides;

c) basic peptides; and

d) basic amino acids, taken by themselves or in combination.

21. The use according to claim 20 wherein the urocanic acid is combined with a histone or globin, AMP, ADP, or ATP, L-histidine, L-arginine, L-lysine, L-hydroxylysine or L-ornithine.

22. The use according to claim 19, 20 or 21, wherein the urocanic acid derivatives are complexes of urocanic acid with histones, peptides, basic amino acids and nucleotides, which are more cytophilic than the alkali metal or alkaline earth metal mineral salts or derivatives.

23. The use according to any one of claims 1 to 22, of also amino acids and peptides or proteins.

24. The use according to claim 23, wherein the amino acids and peptides and proteins are selected from:

1) one or more of the following amino acids:

. L-histidine, L-arginine, L-lysine, L-citrulline, L-ornithine and L-hydroxylysine,

. L-tyrosine, L-phenylalanine and L-tryptophan, L-glutamic acid and L-aspartic acid, L-proline (L-hydroxyproline),

. glycine, alanine, L-valine, L-leucine and L-isoleucine,

. L-serine and L-threonine,

. L-glutamine and L-asparagine,

. L-cysteine, L-methionine and cystine,

2) one or more peptides and proteins which occur naturally in cells, and/or peptides resulting from the acid, basic or enzymatic hydrolysis of polypeptides and/or proteins, scleroproteins and soluble proteins.

25. The use according to claim 24 wherein the peptides and proteins are selected from glutathion,

- silk fibroin in a concentration from 1 to 10%,
- collagen in a concentration from 1 to 10%,
- elastin in a concentration from 1 to 10%,
- hydrophilic keratin
- histone in a concentration from 0.1 to 10%;
- globins (hemoglobins and myoglobins) in a concentration from 0.1 to 10%,
- plasma proteins (for example serum albumin and serum globulins) in a concentration from 0.1 to 10%, and
- partially enzymatically hydrolyzed plasma proteins from blood plasma rich in proteins (about 8%) in a

concentration from 0.1 to 10%.

26. The use according to any one of claims 1 to 25, wherein the concentration of cell protecting compound in the composition is between 0.01% and 10% by weight, relative to the total weight of the medicament or cosmetic composition.

27. The use according to claim 26 wherein the said concentration is between 0.1 and 3% by weight.

28. A compound selected from the group consisting of simple or complex salts of the ribonucleotides with organic bases selected from basic proteins and basic peptides.

29. A compound according to claim 28 in which the protein is histone or globin and the peptide is glutathion.

30. A compound according to claim 28 or 29, wherein the ribonucleotides are selected from:

RIBONUCLEOTIDES

AMP	ADP	ATP
GMP	GDP	GTP
CMP	CDP	CTP
UMP	UDP	UTP
IMP	IDP	ITP
XMP	XDP	XTP

31. A cosmetic or pharmaceutical composition for topical application comprising a compound selected from the group consisting of:

A - simple or complex salts of the ribonucleic acids with organic bases selected from basic proteins and basic peptides, and

B - simple or complex salts of the ribonucleotides with organic bases selected from basic proteins and basic peptides, in a cosmetic or pharmaceutical excipient, vehicle or carrier for topical application.

32. A composition according to claim 31 wherein the concentration of the said compound is 0.01 to 10% by weight of the composition.

33. A composition according to claim 31 or 32 wherein the protein is histone or globin and the peptide is glutathion.

CLAIMS

1. The use in the manufacture of a medicament for protecting skin cells, in particular the Langerhans' cells, from the sun, of at least one compound selected from the group of nucleic acid compounds and derivatives consisting of:

A - ribonucleic acids and their salts with mineral or organic bases;

B - ribonucleotides and their salt-type derivatives with mineral or organic bases; and

C - ribonucleosides.

2. The use of at least one compound selected from the group of nucleic acid compounds and derivatives consisting of:

A - ribonucleic acids and their salts with mineral or organic bases;

B - ribonucleotides and their salt-type derivatives with mineral or organic bases; and

C - ribonucleosides

in a cosmetic composition for protecting the skin cells from the sun.

3. The use according to claim 1 wherein said medicament composition does not contain a synthetic cytotoxic sun filter of the cinnamate or PABA type or their derivatives.

4. The use according to claim 1, 2 or 3 of at